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Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 40, No. 7, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02159-9

Cardiovascular Remodeling Is Greater in Isolated Systolic Hypertension Than in Diastolic Hypertension in Older Adults: The Insufficienza Cardiaca negli Anziani Residenti (ICARE) a Dicomano Study

Riccardo Pini, MD, FACC,* M. Chiara Cavallini, MD,* Francesca Bencini, MD,* Gabriella Silvestrini, MD,* Elisabetta Tonon, MD,* Walter De Alfieri, MD,* Niccolò Marchionni, MD,* Mauro Di Bari, MD, PHD,* Richard B. Devereux, MD, FACC,† Giulio Masotti, MD,* Mary J. Roman, MD, FACC†

Firenze, Italy; and New York, New York

OBJECTIVES We investigated cardiac and vascular remodeling in an unselected older population with either diastolic hypertension (HTN) or isolated systolic hypertension (ISH).

BACKGROUND Isolated systolic hypertension accounts for a substantial proportion of hypertension in individuals older than 65 years and is strongly associated with an increased risk of cardiac and cerebrovascular events. The exact mechanisms underlying the increased risk associated with ISH and elevated pulse pressure (PP), in comparison with HTN, have not been extensively investigated.

METHODS Community-dwelling residents age ≥65 years in a small town in Italy (Dicomano) were enrolled. Untreated subjects considered in this study included 173 normotensive subjects (blood pressure [BP] <140/90 mm Hg), 95 subjects with HTN (diastolic BP ≥90 mm Hg), and 43 subjects with ISH (BP ≥160/<90 mm Hg). All subjects underwent extensive clinical examination, echocardiography, carotid ultrasonography, and carotid applanation tonometry.

RESULTS Subjects with ISH had higher left ventricular (LV) mass, which was independently related to PP but not to systolic or mean pressures. Both carotid wall cross-sectional area and vascular stiffness were greater in ISH patients than in HTN and normal subjects and were independently related to PP but not to systolic BP. In addition, ISH was associated with a higher prevalence of carotid plaque and more extensive carotid atherosclerosis.

CONCLUSIONS In our community-based elderly population, individuals with ISH had higher prevalences of LV hypertrophy and carotid atherosclerosis than subjects with HTN despite lower mean BP. These findings provide potential pathophysiologic mechanisms underlying the associations of ISH and PP with increased risk of cardiovascular morbidity and mortality. (J Am Coll Cardiol 2002;40:1283–9) © 2002 by the American College of Cardiology Foundation

Isolated systolic hypertension (ISH) is associated with aging and accounts for a substantial proportion of hypertension in individuals over age 65 years (1). Isolated systolic hypertension is strongly associated with an increased risk of cardiac and cerebrovascular events (2), exceeding that in comparably aged individuals with diastolic hypertension (HTN) (3). Therefore, pulse pressure (PP) has emerged as a strong predictor of cardiovascular mortality and morbidity in the general population (4–6) as well as in individuals with hypertension (7), myocardial infarction (8), and heart failure (9). Pulse pressure is closely correlated with systolic blood pressure (SBP); however, the few studies that have examined the relative importance of SBP and PP have shown either comparable (7) or independent (5,10) relationships of PP to outcomes after accounting for SBP. The exact mechanisms underlying the increased risk associated with ISH and elevated PP, in comparison with HTN, have not been extensively investigated. Therefore, the present study was designed to evaluate cardiac and vascular anatomy and function in an unselected older population in relation to clinical features and blood pressure (BP) status.

METHODS

Study population. The data were acquired from a population-based survey of heart failure in the community-dwelling older population of Dicomano, a small town near Florence, Italy. From the 899 citizens aged ≥65 years old recorded in the City Registry Office of Dicomano, 864 community-dwelling subjects were eligible for the Insufficienza Cardiaca negli Anziani Residenti (ICARe) a Dicomano study; 614 subjects completed the extensive assessment including home interview, laboratory testing, and

From the *Department of Critical Care Medicine and Surgery-Unit of Gerontology and Geriatrics, University of Firenze and Azienda Ospedaliera Careggi, Firenze, Italy; and the †Department of Medicine, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, New York. Supported, in part, by the Italian Ministry of Scientific and Technological Research (National Special Project on Heart Failure), by the Regional Government of Tuscany, and by the Azienda Ospedaliera Careggi, Firenze, Italy.

Manuscript received July 3, 2001; revised manuscript received May 30, 2002, accepted July 2, 2002.

JACC Vol. 40, No. 7, 2002
October 2, 2002:1283–9

Abbreviations and Acronyms

AI = augmentation index
BP = blood pressure
DBP = diastolic blood pressure
HTN = diastolic hypertension
IMT = intimal-medial thickness
ISH = isolated systolic hypertension
LV = left ventricle/ventricular
MBP = mean blood pressure
PP = pulse pressure
SBP = systolic blood pressure

clinical examination. Further clinical information was gathered from participants' primary physicians, who answered a structured questionnaire about history and treatment of several conditions, including hypertension. The general design of the study has been detailed elsewhere (11). The study was approved by an ad-hoc ethics committee. Patients' informed consents were systematically obtained, and a letter describing the study design was sent to their primary physicians.

BP measurement and diagnosis of hypertension. Blood pressure was measured with the participant supine after 10 min rest. The second and third of three consecutive readings were averaged. Diastolic blood pressure (DBP) was defined as disappearance of the fifth Korotkoff sound.

Subjects on antihypertensive medication were excluded from the present study; participants were grouped by the following criteria: normotensives = BP <140/90 mm Hg; HTN = DBP ≥90 mm Hg; and ISH = SBP ≥160 mm Hg and DBP <90 mm Hg. Subjects with SBP 140 to 159 mm Hg and DBP <90 mm Hg were termed borderline hypertensive; their data were previously published (12). No normotensive subject had been treated for hypertension. Hypertensive subjects never treated for hypertension or off medication for at least one month constituted 95 of 265 HTN subjects and 43 of 67 ISH subjects.

Echocardiography. From two-dimensional guided M-mode echocardiograms, left ventricular (LV) dimensions were measured by American Society of Echocardiography convention; LV mass was calculated by the adjusted American Society of Echocardiography method (13) and indexed for body surface area or height$^{2.7}$. Left ventricular mass/body surface area ≤116 g/m^2 in men and ≤104 m/g^2 in women was considered normal (14). Left ventricular mass/height$^{2.7}$ was considered normal if ≤49.2 g/m$^{2.7}$ in men and ≤46.7 g/m$^{2.7}$ in women (15). Ejection fraction was calculated from apical four-chamber views. Valvular disease was classified significant if moderate-severe stenosis and/or insufficiency was detected by Doppler echocardiography. Of 311 subjects included in the present analysis, 307 (99%) subjects underwent echocardiography; the 34 subjects in whom echocardiographic examination was not performed or was technically limited were older than those with complete data (77 ± 8 years vs. 73 ± 6 years, p = 0.002).

Carotid ultrasonography. As previously described (16,17), two-dimensional-guided M-mode tracings of the distal left common carotid artery were obtained with simultaneous contralateral pressure waveform tracings (see the following text). Measurements included intimal-medial thickness (IMT) of the far wall at end-diastole, and end-diastolic and peak-systolic internal dimensions. Relative wall thickness of the common carotid artery and carotid intimal-medial cross-sectional area were also calculated (17). Both carotid arteries were scanned using two-dimensional imaging to identify the presence of atherosclerotic plaques defined as focal increases in IMT >50% of the surrounding wall; IMT was never measured at the level of a discrete plaque. Plaque number was defined as the number of locations with discrete plaques within both right and left carotid systems. Carotid ultrasound examination was obtained in 306 (98%) subjects in this study; the 40 subjects without carotid examination or with incomplete data due to technically difficult studies were older (75 ± 7 years vs. 73 ± 6 years, p = 0.035) and had higher body mass index (29.24 ± 5.71 kg/m^2 vs. 26.45 ± 4.11 kg/m^2, p = 0.005) than those with complete examination.

Carotid artery stiffness. Carotid pressure waveforms were obtained (18) using a high-fidelity external pressure transducer (Millar Instruments, Inc., Houston, Texas) applied to the skin overlying the common carotid artery pulse. Carotid pulse recording was obtained in 258 (83%) subjects; the 53 subjects in whom it was impossible to obtain a carotid pulse tracing were older (76 ± 6 years vs. 73 ± 6 years, p = 0.003) and had higher body mass index (28.27 ± 5.36 kg/m^2 vs. 26.51 ± 4.17 kg/m^2, p = 0.027) than those with tonometric examination. Brachial artery pressure was measured at the end of the carotid study by cuff and mercury sphygmomanometer with the patient supine. Brachial mean blood pressure (MBP) was derived from SBP and DBP using the following formula: MBP = DBP + ([SBP − DBP] / 3). Because MBP and DBP are nearly identical in capacitance vessels (19), the MBP was assigned to the planimetrically computer-derived MBP of the carotid waveforms, and the DBP was assigned to the diastolic carotid pressure. Carotid artery stiffness was calculated by the pressure-independent stiffness index, Beta, which takes into account the logarithmic relationship between arterial pressure and diameter (20):

$$\text{Beta} = \frac{\ln \frac{P_s}{P_d}}{\frac{(D_s - D_d}{D_d}}$$

where P_s and P_d are the systolic and diastolic carotid pressures and D_s and D_d are the systolic and diastolic carotid diameters, respectively.

Carotid compliance and distensibility were also calculated using the following formulae (21):

Table 1. Characteristics of Normotensive Subjects and Patients With HTN and ISH

	Normotensive (n = 173)	p 1 vs. 2	HTN (n = 95)	p 2 vs. 3	ISH (n = 43)	p 1 vs. 3	p
Age (yrs)	72 ± 6	0.380	73 ± 7	0.008	77 ± 7	<0.0001	<0.0001
Gender (female %)	91 (53%)		48 (51%)		22 (51%)		0.945
BSA (m^2)	1.68 ± 0.19		1.70 ± 0.18		1.65 ± 0.17		0.278
BMI (kg/m^2)	26.58 ± 4.74	0.146	27.69 ± 4.10	0.062	25.77 ± 3.54	0.630	0.037
Heart rate (beats/min)	67 ± 13		70 ± 12		66 ± 16		0.078
Systolic BP (mm Hg)	127 ± 9		159 ± 16		170 ± 9		
Diastolic BP (mm Hg)	78 ± 6		94 ± 5		83 ± 5		
Mean BP (mm Hg)	94 ± 6	<0.0001	116 ± 8	<0.0001	112 ± 5	<0.0001	<0.0001
Pulse pressure (mm Hg)	48 ± 9	<0.0001	65 ± 14	<0.0001	87 ± 9	<0.0001	<0.0001
Glucose (mg/dl)	102 ± 30(171)		105 ± 29(94)		114 ± 39(42)		0.060
Total cholesterol (mg/dl)	230 ± 38(172)		225 ± 45(94)		215 ± 42(42)		0.091
HDL cholesterol (mg/dl)	57 ± 17(172)		57 ± 18(93)		58 ± 16(42)		0.890
LDL cholesterol (mg/dl)	147 ± 37(172)	0.119	137 ± 41(93)	0.871	133 ± 44(42)	0.109	0.032
Stroke, TIA	10 (6%)(171)		5 (5%)		3 (7%)(42)		0.911
Coronary artery disease	20 (12%)(170)		6 (7%)(93)		3 (7%)(41)		0.327
Peripheral vascular disease	12 (7%)(170)		10 (11%)(94)		6 (14%)		0.310
Diabetes	14 (8%)(170)	1.000	7 (7%)(94)	0.119	9 (21%)(42)	0.071	0.024
Former or current smoking	80 (47%)(171)		44 (46%)		18 (42%)		0.843

The superscript number on the right side of the value indicates the sample size if different from what is reported in the column heading.

BMI = body mass index; BP = blood pressure; BSA = body surface area; HDL = high-density lipoprotein; HTN = diastolic hypertension, ISH = isolated systolic hypertension; LDL = low-density lipoprotein; TIA = transient ischemic attack.

$$\text{Compliance} = (\pi \times D_d \times [D_s - D_d]/2)/(PP_c \times 0.133)$$

$$\text{Distensibility} = (2 \times [(D_s - D_d)/D_d])/(PP_c \times 0.133)$$

where PP_c is the pulse pressure in the common carotid artery.

The contribution of reflected pressure waves to central PP was measured by the augmentation index (AI); as proposed by Murgo et al. (22), the amplitude of the reflected wave was divided by the PP. In view of potential attenuation of the reflected wave contribution to the AI by the larger PP found in ISH, a modified AI was calculated by dividing the reflected amplitude wave by MBP.

Statistical analysis. Data are expressed as mean ± SD. Differences among groups were tested by one-way analysis of variance with Dunnett T3 test of homogeneity of variances and the Scheffé post-hoc test for continuous variables. Analysis of covariance was also performed to compare means controlling for age, PP, and SBP. Proportions between groups were compared by chi-square statistics with Bonferroni correction. The relationships between continuous variables were evaluated by linear regression and correlation analyses. Variables significant in univariate analyses were considered as independent variables in multiple regression analyses. Two-tailed $p < 0.05$ was considered significant.

RESULTS

Clinical features of normotensive and hypertensive patients. Demographics, laboratory data, and clinical features of the three groups are compared in Table 1. Subjects with ISH were older than normotensive or HTN subjects but did not differ in gender distribution, height, weight (data not shown), or body surface area. By definition, subjects with ISH had higher PP, but MBP was lower in ISH than in HTN. Lipid profile tended to be most favorable in the ISH group. No differences were found among groups in history of stroke, transient ischemic attack, coronary artery or peripheral vascular diseases, or current or former smoking, but diabetes was more prevalent in subjects with ISH.

Echocardiographic findings in normotensive and hypertensive groups. Left ventricular wall thicknesses increased progressively from normotensive to HTN to ISH subjects (Table 2), without differences in LV internal diameters. As a consequence, absolute and adjusted LV mass and the prevalence of LV hypertrophy showed stepwise increases. The differences in LV wall thickness, mass, and mass index remained significant after adjustment for age but disappeared after adjustment for either SBP or PP. The prevalence of significant valvular disease was similar (14% to 17%, p = NS) in the three groups. Differences in absolute and adjusted LV mass remained significant after exclusion of subjects with significant valvular disease. Left ventricular ejection fraction was similar in the three groups.

Determinants of LV mass. In multivariate analyses, male gender ($\beta = 0.341$, $p < 0.0001$), lower ejection fraction ($\beta = -0.223$, $p < 0.0001$), higher body mass index ($\beta = 0.215$, $p < 0.0001$), and PP ($\beta = 0.207$, $p < 0.0001$) were independent correlates of LV mass (multiple $R^2 = 0.271$, $p < 0.0001$), whereas MBP, SBP, and diabetes did not enter the model, suggesting a stronger influence of PP than SBP on the development of LV hypertrophy. Systolic BP and MBP entered the model when PP was excluded. When categorical variables for BP groups (one with HTN = 1 and normotensive and ISH = 0; the second with ISH = 1 and normotensive and HTN = 0) were substituted for BP in two separate models, ISH remained in the model ($\beta = 0.218$, p <

Table 2. Echocardiographic Characteristics of Normal and Hypertensive Subjects

	Normotensive (n = 153)	p 1 vs. 2	HTN (n = 86)	p 2 vs. 3	ISH (n = 38)	p 1 vs. 3	p
IVSd (mm)	8.0 ± 1.3	0.078	8.4 ± 1.7	0.188	9.0 ± 2.2	0.001	0.001
PWT_d (mm)	7.5 ± 1.1	0.001	8.1 ± 1.4	0.530	8.4 ± 1.4	<0.0001	<0.0001
$LVID_d$ (mm)	51.5 ± 6.0		51.6 ± 6.9		53.0 ± 4.9		0.428
$LVID_s$ (mm)	32.3 ± 6.5		32.4 ± 7.0		32.6 ± 6.4		0.966
LV mass (g)	139 ± 42	0.108	153 ± 49	0.161	170 ± 53	0.002	0.001
LV mass index (g/m^2)	83 ± 23	0.148	89 ± 26	0.026	102 ± 26	<0.0001	<0.0001
LV mass/$height^{2.7}$ ($g/m^{2.7}$)	40 ± 12	0.036	44 ± 13	0.164	49 ± 13	<0.0001	<0.0001
Relative WT	0.29 ± 0.05	0.005	0.32 ± 0.09	0.971	0.32 ± 0.05	0.097	0.002
LV hypertrophy (LVMI)	15 (10%)	0.883	13 (15%)	0.088	13 (34%)	0.002	0.001
LV hypertrophy (LVMH)	28 (18%)	0.003	33 (38%)	1.000	18 (47%)	0.002	<0.0001
Ejection fraction (%)	61 ± 10(162)		60 ± 9(90)		62 ± 8(41)		0.517

The superscript number on the right side of the value indicates the sample size if different from what is reported in the column heading.

HTN = diastolic hypertension; ISH = isolated systolic hypertension; IVS_d = diastolic interventricular septal thickness; LV = left ventricular; $LVID_d$ = left ventricular internal diameter in diastole; $LVID_s$ = left ventricular internal diameter in systole; LVMI = left ventricular mass index; LVMH = left ventricular mass/$height^{2.7}$; PWT_d = diastolic posterior wall thickness; WT = wall thickness.

0.0001) while HTN did not, supporting the importance of ISH, as well as PP, in fostering LV hypertrophy.

Carotid artery structure and stiffness in normotensive and hypertensive groups. Partially by definition, carotid SBP and DBP differed significantly among the three groups, with the widest PP in ISH subjects (Table 3). Carotid IMT was similar in the three groups, while diastolic diameter tended to be highest with ISH. As a consequence, carotid artery cross-sectional area, a surrogate measure of vascular mass, was larger in ISH patients than in the other two groups. The prevalence and number of plaques were highest in the ISH group and intermediate in the HTN group.

There were significant stepwise increases in the stiffness index and in the amplitude of the reflected wave from normotensive to HTN to ISH subjects. However, when the AI was calculated by dividing the reflected wave amplitude by the PP as recommended by Murgo et al. (22), there was no difference among groups in AI. In contrast, when the AI was calculated using MBP, the augmentation was significantly higher in subjects with ISH than in the other two groups and higher in subjects with HTN than in normotensives. Carotid compliance and distensibility were similarly lower in the subjects with HTN and ISH than in normotensive subjects.

Determinants of carotid artery structure and function. In multivariate analysis, only male gender and higher PP were independent correlates of increased carotid cross-sectional area (Table 4). The number of carotid plaques was independently related to PP, male gender, diabetes, and SBP. Although SBP bore a negative relationship to the number of plaques, SBP exhibited a positive correlation when PP was excluded from the model although the model was weakened (multiple R^2 = 0.193), supporting the hypothesis that PP is a stronger correlate than SBP. In multivariate analysis, only PP, age, MBP, and absolute

Table 3. Carotid Artery Pressures, Structure, and Stiffness in Normotensive and Hypertensive Subjects

	Normotensive (n = 169)	p 1 vs. 2	HTN (n = 95)	p 2 vs. 3	ISH (n = 42)	p 1 vs. 3	p
Systolic BP (mm Hg)	124 ± 17(152)		142 ± 19(72)		154 ± 23(34)		
Diastolic BP (mm Hg)	74 ± 9(152)		83 ± 11(72)		73 ± 9(34)		
Mean BP (mm Hg)	91 ± 10(152)	<0.0001	103 ± 13(72)	0.472	100 ± 11(34)	<0.0001	<0.0001
PP (mm Hg)	50 ± 14(152)	0.001	59 ± 14(72)	<0.0001	81 ± 21(34)	<0.0001	<0.0001
IMT (mm)	0.83 ± 0.15		0.83 ± 0.16(89)		0.89 ± 0.17(40)		0.875
Diastolic diameter (mm)	5.90 ± 0.84(157)	0.326	6.09 ± 0.96(77)	0.167	6.44 ± 1.07(37)	0.006	0.005
Systolic diameter (mm)	6.76 ± 0.87(157)	0.790	6.85 ± 0.96(77)	0.029	7.35 ± 1.17(37)	0.003	0.003
Systolic expansion (%)	15 ± 5(157)	0.006	13 ± 4(77)	0.209	14 ± 5(37)	0.882	0.006
RWT	0.29 ± 0.06(156)		0.28 ± 0.07(77)		0.28 ± 0.07(37)		0.588
Cross-sectional area (mm^2)	17.81 ± 4.78(156)	0.967	17.98 ± 4.19(77)	0.023	20.60 ± 5.48(37)	0.006	0.005
Plaque (%)	108 (64%)(168)	0.163	72 (76%)	0.773	36 (86%)	0.034	0.010
Plaque number	2 ± 2(168)	0.933	2 ± 2	0.001	3 ± 2	<0.0001	<0.0001
Beta stiffness index	3.97 ± 1.93(146)	0.008	4.99 ± 2.33(67)	0.012	6.42 ± 3.03(32)	<0.0001	<0.0001
Compliance ($m^2kPa^{-1}\cdot10^{-7}$)	12.6 ± 5.1(146)	<0.0001	9.3 ± 3.1(67)	0.915	8.9 ± 5.3(32)	<0.0001	<0.0001
Distensibility ($kPa^{-1}\cdot10^{-3}$)	47.7 ± 20.1(146)	<0.0001	33.1 ± 14.8(67)	0.277	26.9 ± 12.7(32)	<0.0001	<0.0001
Reflected wave (mm Hg)	14 ± 9(151)	0.015	18 ± 10(71)	0.005	25 ± 14(34)	<0.0001	<0.0001
AI (corrected for PP)	0.26 ± 0.14(151)		0.30 ± 0.12(71)		0.30 ± 0.15(34)		0.058
AI (corrected for MBP)	0.15 ± 0.09(151)	0.265	0.17 ± 0.08(71)	0.001	0.25 ± 0.13(34)	<0.0001	<0.0001

The superscript number on the right side of the value indicates the sample size if different from what is reported in the column heading.

AI = augmentation index; BP = blood pressure; HTN = diastolic hypertension; IMT = intimal-medial thickness; ISH = isolated systolic hypertension; MBP = mean blood pressure; PP = pulse pressure; RWT = carotid relative wall thickness.

Table 4. Independent Correlates of Carotid Anatomy and Stiffness

	B	SE	β	p
Cross-sectional Area: Multiple R = 0.394 (R^2 = 0.155)				
Male gender	2.858	0.576	0.295	<0.0001
Pulse pressure	0.071	0.016	0.266	<0.0001
Constant	18.733	1.269		
Not entering the model: age, diabetes, and systolic and mean pressures.				
Carotid Plaque Number: Multiple R = 0.469 (R^2 = 0.220)				
Pulse pressure	0.059	0.013	0.542	<0.0001
Male gender	0.948	0.221	0.242	<0.0001
Diabetes	0.975	0.395	0.141	0.014
Systolic pressure	−0.021	0.011	−0.230	0.046
Constant	2.782	0.930		
Not entering the model: age, body mass index, reflected wave, augmentation index corrected for mean pressure.				
Beta: Multiple R = 0.591 (R^2 = 0.349)				
Pulse pressure	0.061	0.011	0.465	<0.0001
Age	0.060	0.022	0.152	0.007
Mean pressure	−0.035	0.012	−0.183	0.005
Reflected wave	0.038	0.017	0.173	0.025
Constant	−0.434	1.850		
Not entering the model: gender, LDL cholesterol, diabetes, systolic pressure, augmentation index corrected for mean pressure.				

LDL = low-density lipoprotein; SE = standard error of B coefficient; β = standardized B coefficient.

reflected wave amplitude were independent correlates of the stiffness index; of note, when PP was included in the model, MBP was negatively correlated with the stiffness index (Table 4). When PP was excluded from the model, the overall strength was reduced (multiple R^2 = 0.254), and MBP did not enter the model, while the absolute reflected wave amplitude became the strongest independent correlate of the stiffness index. When BP values were replaced by BP groups as categorical variables in two separate models, ISH entered the model (β = 0.147, p = 0.014) while HTN did not.

DISCUSSION

This study represents the first assessment of the effects of heightened PP (manifest as ISH) on LV geometry and carotid anatomy and stiffness in comparison with unselected normotensive and diastolic hypertensive elderly individuals. The study provides evidence that, in a community-based population of subjects aged ≥65 years, LV hypertrophy tends to be more prevalent and carotid atherosclerosis is more extensive in subjects with ISH than in those with HTN, despite lower MBP. Furthermore, ISH was associated with greater vascular remodeling and stiffening than was HTN.

LV hypertrophy. In the present study, PP was the only independent predictor of LV mass among the various BP variables. This association, along with the well-established increase in cardiovascular events attributable to LV hypertrophy (23,24), provides one potential mechanism whereby ISH and PP might increase risk. Interestingly, although LV mass eliminated SBP from the model predicting adverse cardiovascular outcome (25), PP has been shown to predict cardiovascular risk independently of electrocardiographic LV hypertrophy (26). Comparable to previous studies, the presence of ISH was not associated with LV systolic dysfunction (27,28).

Elevated PP, SBP, or both predispose to LV hypertrophy, whereas lower values of DBP can potentially reduce coronary perfusion. The similar prevalence of coronary and cerebrovascular disease despite the greater LV hypertrophy in the ISH group may reflect survival bias in this group due to a higher incidence of death from myocardial infarction or stroke, as previously reported in epidemiologic studies on ISH (29,30). Such a survival bias is in agreement with the tendency toward a more favorable lipid profile in our older group with ISH.

Increases in LV mass and prevalence of LV hypertrophy in individuals with ISH compared with age-matched normotensive individuals have been amply documented (27,31,32). Only one previous study has compared echocardiographic findings in elderly individuals with ISH to those with HTN; in a population-based Dutch study, Heesen et al. (32) found LV mass index to be similar in 97 subjects with ISH and 50 subjects with HTN (98 vs. 92 g/m^2) with no difference in relative wall thickness. Comparable measurements in the current population (102 and 89 g/m^2) were found to be significantly different. The prevalence of LV hypertrophy (defined as LV mass index ≥125 g/m^2) was similar in the Dutch study (9% in both ISH and HTN), whereas ISH subjects in the present study had twofold increases in LV hypertrophy by the same criterion (20% vs. 9%, p < 0.0001) as well as by gender-specific criteria (34% vs. 15%, p = 0.088). The explanation for the differences between the two studies is not readily apparent, although individuals in the Dutch study were younger and had higher average systolic and diastolic pressures.

Vascular remodeling and atherosclerosis. Compared with participants with HTN, those with ISH exhibited greater carotid wall volume and vascular stiffness despite similar carotid MBP. Carotid atherosclerosis in this elderly population was most prevalent in the ISH group. These results support the hypothesis that elevated PP causes fatigue and fracture of elastic elements of arterial wall. The similarity in central MBP between the two hypertensive groups indicates that the increased arterial stiffness in ISH cannot be attributed to higher distending pressure. Of note, when all BP measurements were included in multiple regression models of carotid anatomy and function, only PP, but not SBP or DBP, entered the model. Boutouyrie et al. (33) have demonstrated that during long-term antihypertensive treatment, regression of carotid artery wall hypertrophy was dependent on reduction of PP, confirming the relationship between PP and carotid remodeling. Recently, Domanski et al. (34) suggested that the associations of increased PP with stroke and total mortality are due to increased arterial

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stiffness. Our data support this hypothesis by providing direct evidence that increased PP is associated with stiffer arteries and early return of reflected waves.

Several previous studies have examined conduit artery structure and atherosclerosis in relation to ISH and PP; however, none have compared findings to those with HTN. In the Cardiovascular Health Study, age-adjusted common carotid mean and maximum IMT as well as the proportion with significant carotid stenosis were higher with ISH (28). Among subjects with HTN, Khattar et al. (35) found PP to predict carotid IMT better than SBP. In a French population-based study, PP was associated with a longitudinal change in carotid IMT, but its predictive value was not compared with SBP (36). Likewise, Boutouyrie et al. (37) found carotid IMT to be strongly influenced by carotid PP but not MBP.

Potential study limitations. The major limitation of this study is its cross-sectional design, which precludes determining whether the increased prevalence of carotid atherosclerosis in ISH patients is a consequence of the higher PP or if the higher PP is the result of increased carotid stiffness due to the atherosclerosis. Moreover, while cardiac and vascular remodeling reflect changes developed over years or even decades, the lack of cumulative BP measurements may weaken the association between BP and cardiac and vascular anatomy and function.

Our study population was defined as having HTN and ISH based on clinical BP measurements; this selection criterion, in the absence of ambulatory BP monitoring, does not identify patients with white-coat hypertension, which, in a Systolic Hypertension in Europe Trial subgroup, constituted about one-fourth of patients with ISH (38). However, because white-coat ISH patients have less cardiac and vascular remodeling than sustained ISH patients, their exclusion might actually strengthen the association between PP and LV and carotid changes found in the present study.

It is possible that our population is not entirely representative of elderly individuals with ISH. However, our study is community-based with a high rate of participation (80% of eligible individuals) (11). Furthermore, the prevalence of ISH in our study (11% of subjects with cardiologic assessment) is comparable to that seen in other populations (2,28).

Clinical implications. Our data demonstrating increased prevalences of LV hypertrophy and carotid atherosclerosis in older patients with ISH provide potential pathophysiologic mechanisms underlying associations of ISH and PP with increased risk of cardiovascular morbidity and mortality. Both our data and previous studies (6,10,33) suggest that hypertensive treatment should be targeted to reduce arterial stiffness and PP as well as SBP.

Reprint requests and correspondence: Dr. Riccardo Pini, Unit of Gerontology and Geriatrics, Via delle Oblate 4, 50141 Firenze, Italy. E-mail: rpini@unifi.it.

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